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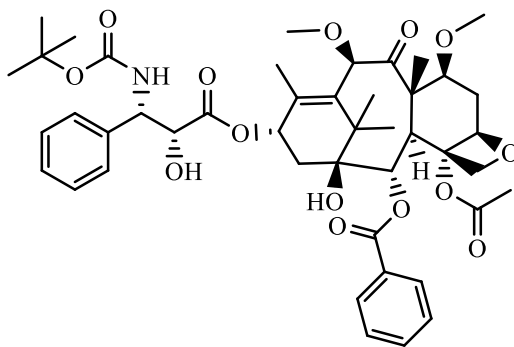


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Process For The Preparation Of Anti-neoplastic Agent

The present invention provides a process for the preparation of (2 α ,5 β ,7 β ,10 β ,13 α)-4-acetoxy-13-((2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl)oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate compound of formula-1 and intermediates thereof.



Formula-1

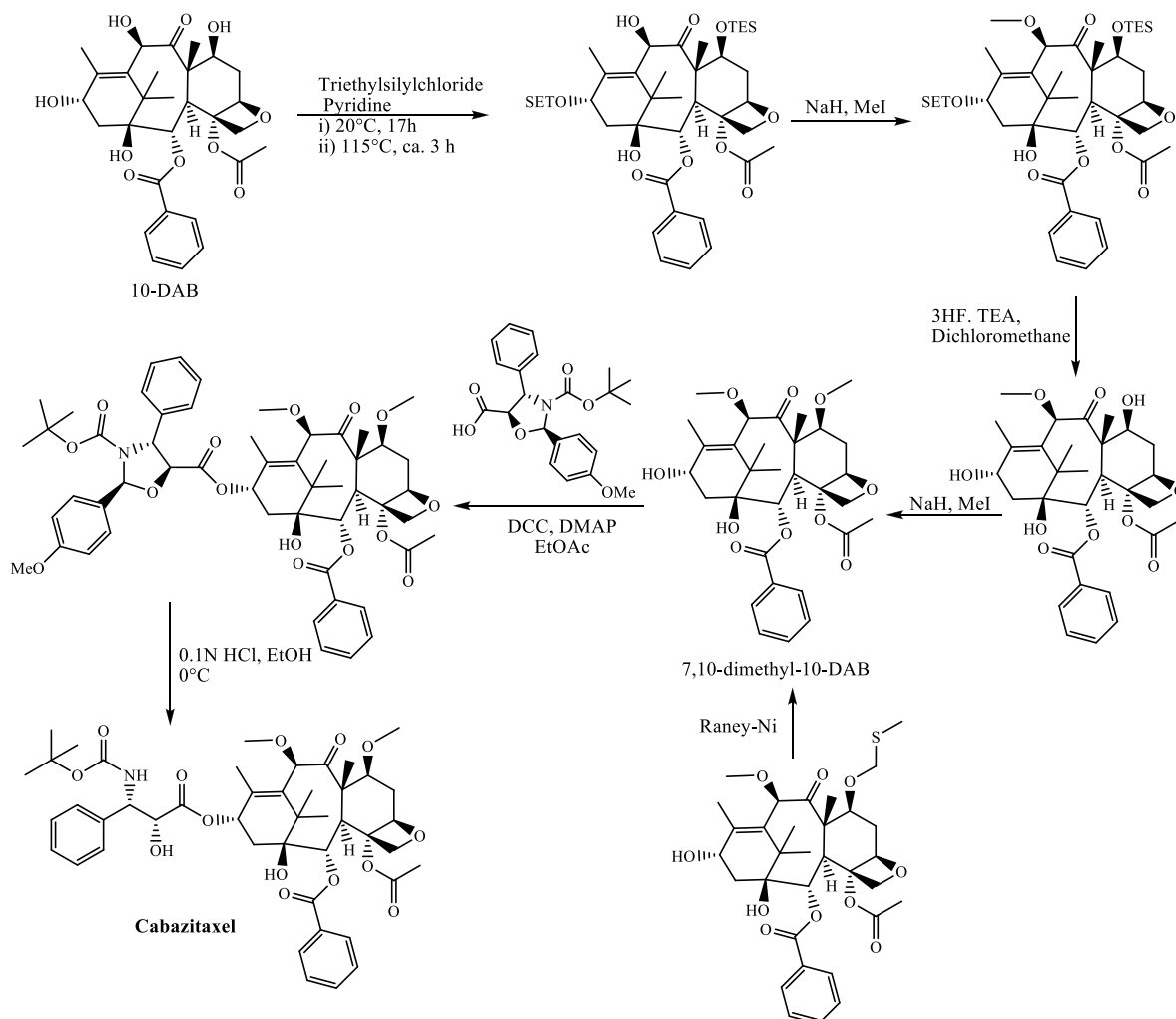
(2 α ,5 β ,7 β ,10 β ,13 α)-4-acetoxy-13-((2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl)oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate is commonly known as Cabazitaxel. Jevtana® is an injectable antineoplastic medicine whose active pharmaceutical ingredient (API), Cabazitaxel, belongs to the taxane class and is closely related in both chemical structure and mode of action to the anticancer drugs paclitaxel and docetaxel. Cabazitaxel is prepared by semi-synthesis from 10-deacetylbaaccatin III (10-DAB) that is extracted from yew tree needles.

Cabazitaxel is a dimethyl derivative of Docetaxel which itself is semi-synthetic and was originally developed by Rhone-Poulenc Rorer. It was approved by the U.S. Food and Drug Administration (FDA) for the treatment of hormone-refractory prostate cancer. Cabazitaxel is a microtubule inhibitor.

US 5,847,170 (hereinafter referred as '170' patent) discloses Cabazitaxel and its preparation methods. The entire content of this patent is incorporated herein by reference. One of the methods described in '170' patent involves the step-wise methylation of 10-deacetylbaaccatin III (10-DAB) to provide key intermediate 4 α -acetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,13 α -dihydroxy-7 β ,10 β -dimethoxy-9-oxo-11-taxene (7,10-dimethoxy-10-DAB). The intermediate 7,10-dimethoxy-10-DAB is coupled with the protected side chain,

and the oxazolidine protecting group is then removed from the side chain to give Cabazitaxel. The process disclosed in the said '170' patent is schematically represented in the below mentioned scheme-A.

Scheme-A:



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There are several disadvantages with the step-wise methylation process:

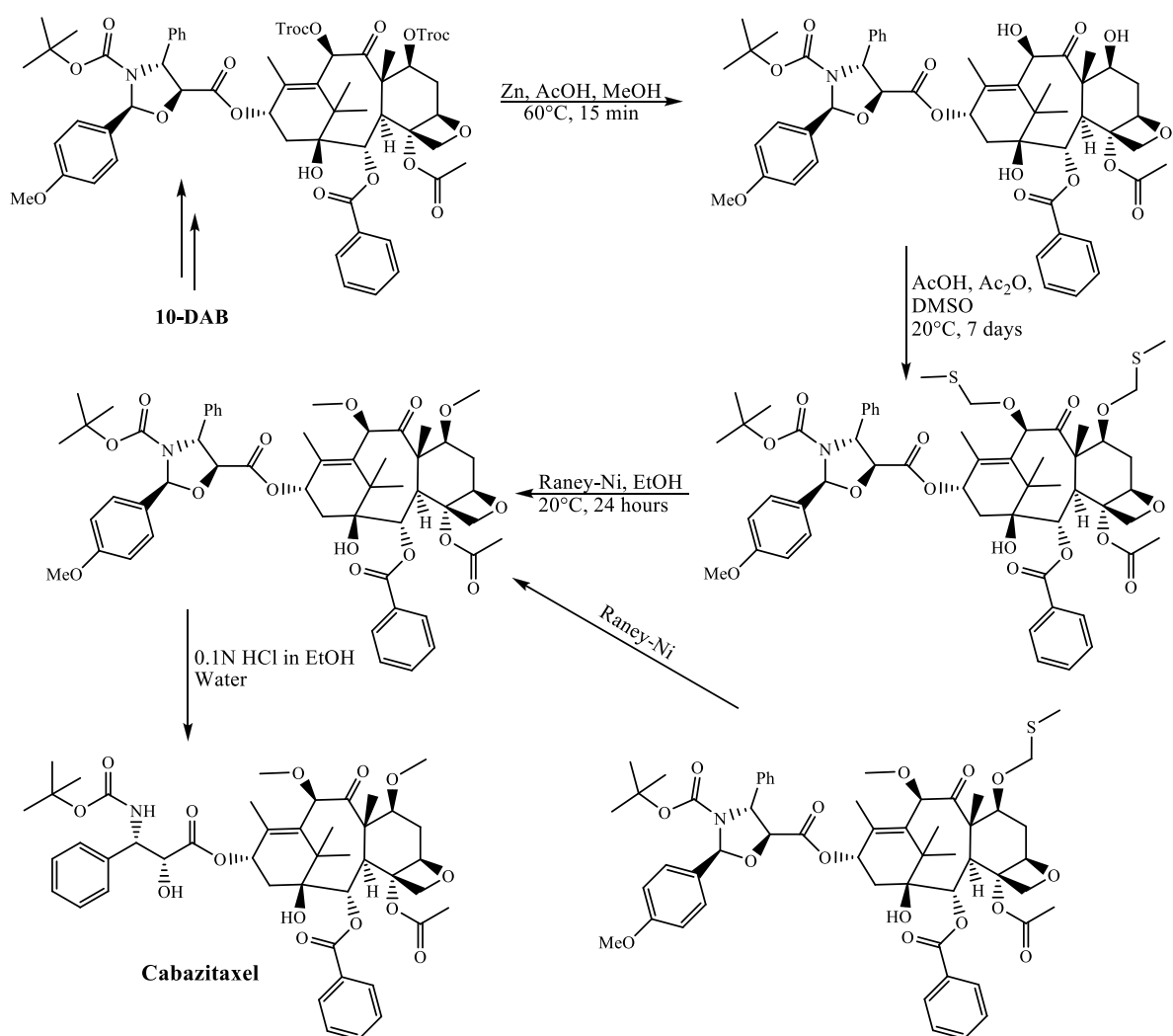
- The said process involves number of steps for the dimethylation of 10-DAB intermediate. Hence the process is not commercially viable.
- The protection of the hydroxyl group at position 13 is needed which is not economical, since an additional molar equivalent of silylating reagent and an additional molar equivalent of desilylating agent are required.

10

- The yield for the methylation at position-10 with methyl iodide/NaH to give the corresponding 10-methyl-7,13-diTES-10-DAB is low.
- The yield for the removal of both silyl protecting groups of 10-methyl-7,13-diTES-10-DAB with HF/triethylamine to give 10-methyl- 10-DAB is low.

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Another method disclosed in '170' patent for the dimethylation of 10-DAB intermediate is the bis-methylthiomethoxy (MTM) route, which is shown in scheme-B.

Scheme-B:

10

However, 7,10-bis-MTM derivatives of 10-DAB are not directly accessible from 10-DAB itself when they are formed using Ac_2O , DMSO (Pummerer reaction). Because these conditions lead to concomitant oxidation of the hydroxyl group at position-13 to the

corresponding ketone. Furthermore, the dimethylthiomethylation of hydroxyl groups at positions 7 and 10 is very slow and proceeds in low yield.

CN 102285947A reported the synthesis of 7,10-dimethoxy-10-DAB by methylating
 5 the hydroxy groups at C₇ and C₁₀ positions in 10-DAB simultaneously to furnish 7,10-dimethoxy-10-DAB, which was then coupled with a protected (3R,4S)- β -lactam followed by deprotection of the 2'-OH to provide Cabazitaxel in very low yield (17.8%).

Hence, there is still a need in the art for the development of an improved process for the preparation of Cabazitaxel and its 7,10-dimethoxy-10-DAB intermediate.

10

The term “suitable solvent” used in the present invention refers to “hydrocarbon solvents” such as n-pentane, n-hexane, n-heptane, cyclohexane, petroleum ether, benzene, toluene, xylene and the like; “ether solvents” such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether, 1,2-dimethoxy ethane, tetrahydrofuran, 1,4-dioxane
 15 and the like; “ester solvents” such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert-butyl acetate and the like; “polar-aprotic solvents such as dimethylacetamide, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone (NMP) and the like; “chloro solvents” such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; “ketone solvents” such as
 20 acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; “nitrile solvents” such as acetonitrile, propionitrile, isobutyronitrile and the like; “alcohol solvents” such as methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, tert-butanol and the like; “polar solvents” such as water; acetic acid, formic acid and/or their mixtures.

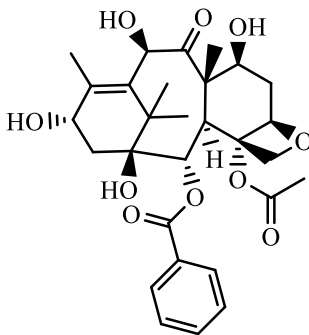
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The term “suitable base” used in the present invention refers to inorganic bases selected from “alkali metal carbonates” such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate and the like; “alkali metal bicarbonates” such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium bicarbonate and the like; “alkali metal hydroxides” such as sodium hydroxide, potassium hydroxide, lithium hydroxide
 30 and the like; “alkali metal alkoxides” such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, sodium tert-butoxide, potassium tert-butoxide, lithium tert-

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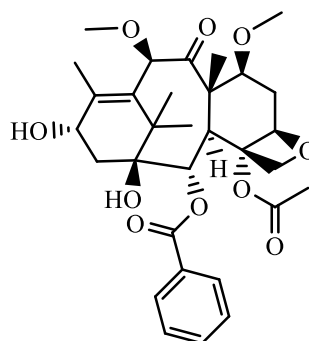
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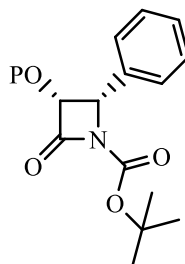
Formula-2

by treating it with a suitable methylating agent in presence of a suitable base in a suitable solvent to provide 7,10-dimethoxy-10-DAB compound of formula-3,



Formula-3

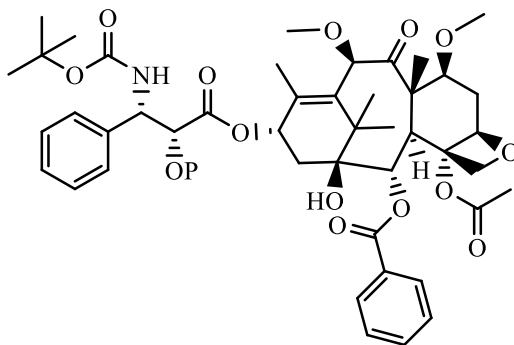
- b) reacting the compound of formula-3 with protected (3R,4S)- β -lactam compound of general formula-4



Formula-4

wherein 'P' is hydroxy protecting group;

in a suitable solvent optionally in presence of a suitable coupling agent and/or a suitable base to provide protected intermediate compound of general formula-5,



Formula-5

- c) deprotecting the compound of general formula-5 by treating it with a suitable deprotecting agent in a suitable solvent to provide compound of formula-1.

Wherein, in step-a) the suitable methylating agent is selected from methyl iodide, dimethyl sulfate, dimethyl carbonate, trimethyloxonium tetrafluoroborate ($\text{Me}_3\text{O} \cdot \text{BF}_4$),

methyl methane sulfonate (MeOMs), methyl trifluoromethanesulfonate (MeOTf), methyl toluene sulfonate (MeOTs) and the like; the suitable base is selected from alkali metal hydroxides, alkali metal carbonates, alkali metal bicarbonates, alkali metal amides, organolithium bases or their mixtures;

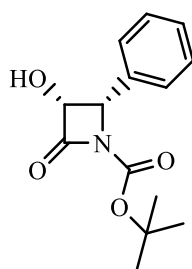
5 In step-b) the suitable coupling agent is selected from N,N'-dicyclohexylcarbodiimide (DCC), N,N'-diisopropylcarbodiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) or its hydrochloride salt, alkyl or aryl chloroformates such as methyl chloroformate, ethyl chloroformate, phenyl chloroformate, benzyl chloroformate, diphenylphosphoroazide (DPPA), thionyl chloride, oxalyl chloride, phosphorous
10 pentachloride and the like, wherein the carbodiimides are used optionally in combination with 1-hydroxy-7-azatriazole (HOAt), 1-hydroxybenzotriazole (HOBt), 1-hydroxy-1H-1,2,3-triazole-4-carboxylate (HOCT), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), N-hydroxysuccinamide (HOSu), N-hydroxysulfosuccinimide (Sulfo-NHS); the suitable base is selected from organic bases, organosilicon bases,
15 organolithium bases, alkali metal hydrides, alkali metal amides and the like;

In step-c) the suitable deprotecting agent is selected depending upon the type of protecting group employed. The suitable deprotecting agent in the present invention is selected from but not limited to acids such as hydrofluoric acid, hydrochloric acid,
20 hydrobromic acid, sulfuric acid, nitric acid, aq.phosphoric acid, acetic acid, trifluoroacetic acid, alkyl/aryl sulfonic acids such as methane sulfonic acid, ethane sulfonic acid, benzene sulfonic acid, p-toluene sulfonic acid and the like; acetyl chloride in combination with alcohols; bases such as alkali metal hydroxides, alkali metal carbonates, cesium carbonate/imidazole, alkali metal bicarbonates; sodium bisulfate, tetra-n-butylammonium
25 fluoride (TBAF), ammonia, cerium(IV) ammonium nitrate (CAN), Fe or Zn in combination with HCl, acetic acid or NH₄Cl; organic bases, pyridine-HF, pyridine-THF and the like; hydrogenating agents such as Pd/C, Pd(OH)₂/C (Pearlman's catalyst), palladium acetate, platinum oxide, platinum black, sodium borohydride, Na-liq.NH₃, Raney-Ni, tri(C₁-C₆)alkylsilanes, tri(C₁-C₆)alkylsilyl halides and the like;

In step-a) to step-c) the suitable solvent is independently selected from ether solvents, ester solvents, chloro solvents, hydrocarbon solvents, polar solvents, polar-aprotic solvents, ketone solvents, alcohol solvents, nitrile solvents, acetic acid, formic acid or their mixtures.

5 In the present invention, the suitable hydroxy protecting group is selected from but not limited to benzyloxycarbonyl (Cbz), tert-butyloxycarbonyl (Boc), acetyl (Ac), trichloroacetyl, trifluoroacetyl (TFA), 1-ethoxyethyl (EE), benzoyl (Bz), benzyl (Bn), p-methoxybenzyl (PMB), methylthiomethyl (MTM), pivaloyl (Piv), trityl (triphenylmethyl or Tr), methoxy-iso-propanyl, tri(C₁-C₆ straight chain or branched chain alkyl)silyl groups such
10 as trimethyl silyl (TMS), tri-ethylsilyl (TES), triisopropylsilyl (TIPS), tri-isopropylsilyloxymethyl (TOM), tert-butyl-dimethylsilyl (TBS or TBDMS), tert-butyl-biphenylsilyl (TBDIPS), furanidinyl, dihydropyran (DHP), tetrahydropyran (THP), trichloroethoxycarbonyl (Troc) and the like.

15 The second aspect of the present invention provides a process for the preparation of (2 α ,5 β ,7 β ,10 β ,13 α)-4-acetoxy-13-((2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl}oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate compound of formula-1, comprising of reacting the 7,10-dimethoxy-10-DAB compound of formula-3 with (3R,4S)-tert-butyl 3-hydroxy-2-oxo-4-phenylazetidine-1-carboxylate
20 compound of formula-6



Formula-6

in a suitable solvent optionally in presence of a suitable coupling agent and/or a suitable base to provide compound of formula-1.

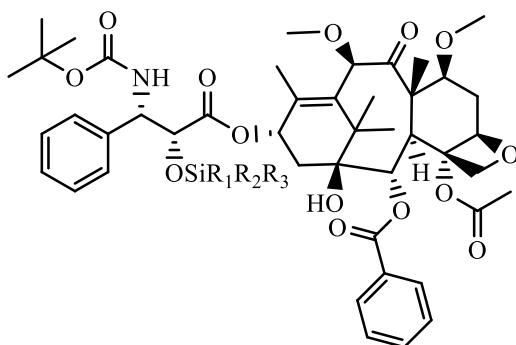
25 Wherein, the suitable coupling agent, the suitable base and the suitable solvent are same as defined in step-b) of the first aspect of the present invention.

The third aspect of the present invention provides a process for the preparation of 7,10-diemthyl-10-DAB compound of formula-3, comprising of methylating the 10-deacetylbaccatin III compound of formula-2 by treating it with a suitable methylating agent in presence of alkali metal hydroxide in a suitable solvent to provide 7,10-diemthyl-10-DAB compound of formula-3.

Wherein, the suitable methylating agent and the suitable solvent are same as defied for step-a) of the first aspect of the present invention.

A preferred embodiment of the present invention provides a process for the preparation of 7,10-dimethoxy-10-deacetylbaccatin compound of formula-3, comprising of methylation of 10-deacetylbaccatin III compound of formula-2 by treating it with dimethyl sulfate in presence of sodium hydroxide in a mixture of tetrahydrofuran and water to provide compound of formula-3.

The fourth aspect of the present invention provides a process for the preparation of (2 α ,5 β ,7 β ,10 β ,13 α)-4-acetoxy-13-((2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl)oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate compound of formula-1, comprising of deprotecting the trialkylsilyl protected intermediate compound of general formula-5'

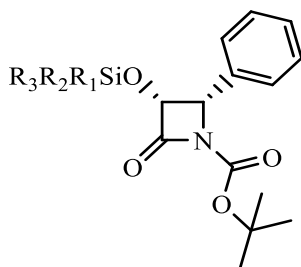


Formula-5'

wherein, R₁, R₂ & R₃ are independently selected from C₁-C₆ straight chain or branched chain alkyl group; preferably methyl, ethyl, isopropyl, tert-butyl; with a suitable silyl deprotecting agent in a suitable solvent to provide compound of formula-1.

Wherein, the suitable silyl deprotecting agent is selected from sodium bisulfate, NaOH/methanol, tetra-n-butylammonium fluoride (TBAF), pyridine-HF, pyridine-THF and the like; the suitable solvent is selected from ether solvents, ester solvents, chloro solvents, hydrocarbon solvents, polar solvents, polar-aprotic solvents, ketone solvents, alcohol solvents, nitrile solvents, acetic acid, formic acid or their mixtures.

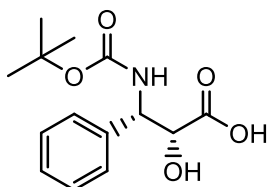
The trialkylsilyl protected intermediate compound of general formula-5' used in the fourth aspect of the present invention can be synthesized by reacting the 7,10-dimethyl-10-DAB compound of formula-3 with trialkylsilyl protected (3R,4S)- β -lactam compound of general formula-4'



Formula-4'

in a suitable solvent optionally in presence of a suitable coupling agent and/or a suitable base to provide compound of general formula-5'.

The fifth aspect of the present invention provides a process for the preparation of (2 α ,5 β ,7 β ,10 β ,13 α)-4-acetoxy-13-((2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl)oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate compound of formula-1, comprising of reacting the 7,10-dimethoxy-10-DAB compound of formula-3 with (2R,3S)-3-(tert-butoxycarbonylamino)-2-hydroxy-3-phenylpropanoic acid compound of formula-7



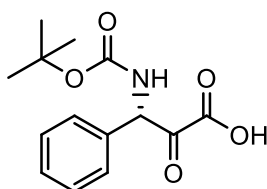
Formula-7

in presence of a suitable coupling agent optionally in combination with a suitable base in a suitable solvent to provide compound of formula-1.

Wherein, the suitable coupling agent, the suitable base and the suitable solvent are same as defined in step-b) of the first aspect of the preset invention.

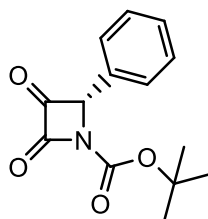
5 The sixth aspect of the present invention provides a novel process for the preparation of (2 α ,5 β ,7 β ,10 β ,13 α)-4-acetoxy-13-((2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl)oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate compound of formula-1, comprising of;

10 a) Reacting the 7,10-dimethoxy-10-DAB compound of formula-3 with (S)-3-(tert-butoxy carbonylamino)-2-oxo-3-phenylpropanoic acid compound of formula-8



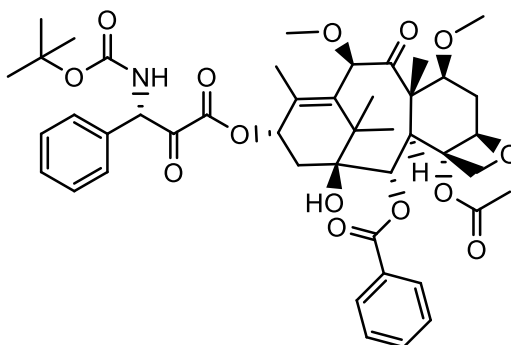
Formula-8

or (S)-tert-butyl 2,3-dioxo-4-phenylazetidine-1-carboxylate compound of formula-9



Formula-9

15 in a suitable solvent optionally in presence of a suitable coupling agent and/or a suitable base to provide keto ester compound of formula-10,



Formula-10

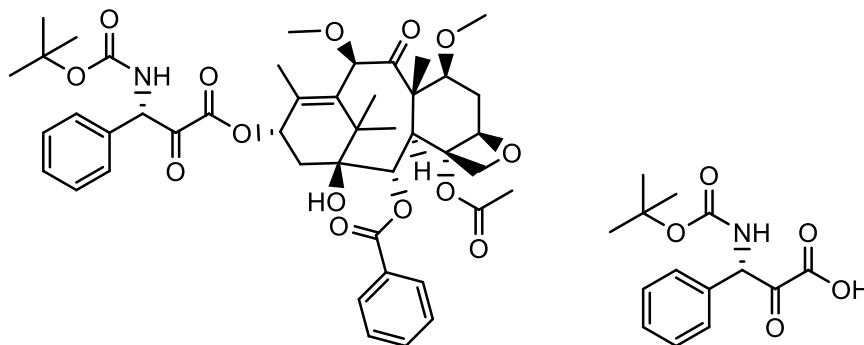
b) reducing the compound of formula-10 with a suitable reducing agent in a suitable solvent to provide compound of formula-1.

Wherein, in step-a) the suitable coupling agent, the suitable base and the suitable solvent are same as defined in step-b) of the first aspect of the present invention;

In step-b) the suitable reducing agent is selected from β -chlorodiisopinocampheyl borane (DIP chloride), borane-THF, borane-DMS optionally in combination with a chiral catalyst like (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo(1,2-c)(1,3,2)oxazaborole (herein after referred as "R-methyl CBS") or R-butyl CBS or R-phenyl CBS and the like; and the suitable solvent is selected from alcohol solvents, ester solvents, ether solvents, polar solvents, hydrocarbon solvents, chloro solvents, ketone solvents, polar-aprotic solvents, acetic acid, formic acid or their mixtures.

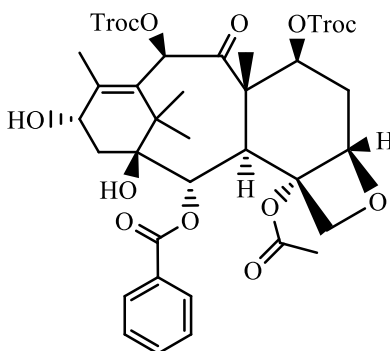
The 10-deacetylbaccatin III (10-DAB) compound of formula-2, protected (3R,4S)- β -lactam compound of general formula-4, (3R,4S)-tert-butyl 3-hydroxy-2-oxo-4-phenylazetidine-1-carboxylate compound of formula-6, (2R,3S)-3-(tert-butoxycarbonyl amino)-2-hydroxy-3-phenylpropanoic acid compound of formula-7 and (S)-tert-butyl 2,3-dioxo-4-phenylazetidine-1-carboxylate compound of formula-9 used in the present invention are commercially available or they can be prepared by any of the synthetic methods described in the literature.

The seventh aspect of the present invention provides novel intermediate compounds which are useful for the preparation of (2 α ,5 β ,7 β ,10 β ,13 α)-4-acetoxy-13-((2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl)oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate compound of formula-1. The said novel intermediate compounds are represented by the below mentioned structural formulae;



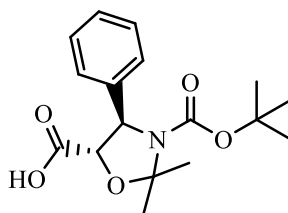
The eighth aspect of the present invention provides a process for the preparation of (2 α ,5 β ,7 β ,10 β ,13 α)-4-acetoxy-13-({(2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl}oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate compound of formula-1, comprising of;

- 5 a) Reacting the 7,10-di-Troc-10-deacetylbaaccatin-III compound of formula-11



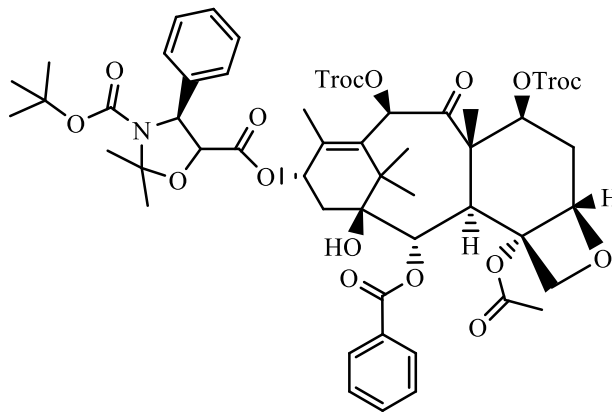
Formula-11

with (4R,5S)-3-(tert-butoxycarbonyl)-2,2-dimethyl-4-phenyloxazolidine-5-carboxylic acid compound of formula-12



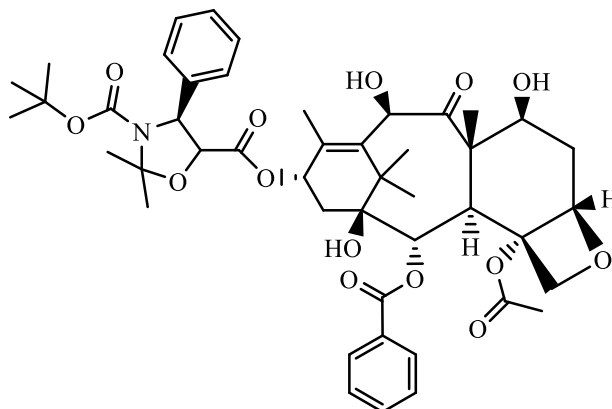
Formula-12

in a suitable solvent and in presence of a suitable coupling agent and/or a suitable base to provide compound of formula-13,



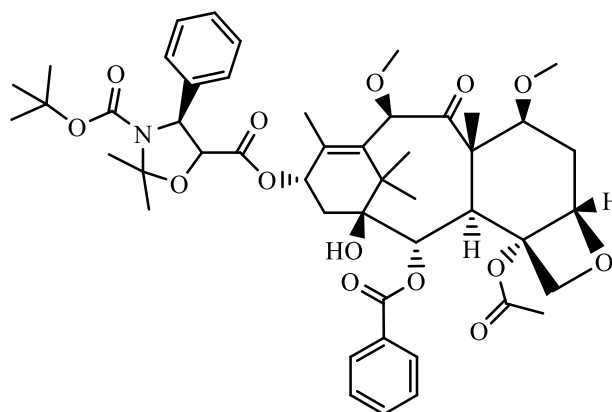
Formula-13

- b) deprotecting the compound of formula-13 by treating it with a suitable Troc-deprotecting agent in a suitable solvent to provide compound of formula-14,



Formula-14

- 5 c) methylating the compound of formula-14 by reacting it with a suitable methylating agent in presence of a suitable base in a suitable solvent to provide compound of formula-15,



Formula-15

- d) treating the compound of formula-15 with a suitable deprotecting agent in a suitable solvent to provide compound of formula-1.

Wherein, in step-a) the suitable coupling agent, the suitable base and the suitable solvent are same as defined in step-b) of the first aspect of the present invention;

- 15 In step-b) the suitable Troc-deprotecting agent is selected from but not limited to Zn/HCl, Zn/NH₄Cl, Zn/acetic acid, Zn-Cu/acetic acid, tetrabutylammonium fluoride (TBAF) and the like; the suitable solvent is selected from alcohol solvents, ester solvents, ether solvents, polar solvents, hydrocarbon solvents, chloro solvents, ketone solvents, polar-aprotic solvents, nitrile solvents or their mixtures.

In step-c) the suitable methylating agent, the suitable base and the suitable solvent are same as defined in step-a) of the first aspect of the present invention;

In step-d) the suitable deprotecting agent is selected from but not limited to sodium bisulfate, inorganic/organic acids such as hydrochloric acid, hydrofluoric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, formic acid, acetic acid, trifluoroacetic acid, trifluoromethanesulfonic acid, alkyl/aryl sulfonic acids such as methane sulfonic acid, ethane sulfonic acid, benzene sulfonic acid, p-toluene sulfonic acid and the like; trimethylsilyl trifluoromethanesulfonate (TMSOTf) in combination with organic/inorganic acids as defined above; the suitable solvent is selected from ether solvents, hydrocarbon solvents, ester solvents, alcohol solvents, chloro solvents, polar solvents, polar-aprotic solvents, ketone solvents, nitrile solvents or their mixtures.

A preferred embodiment of the present invention provides a process for the preparation of (2 α ,5 β ,7 β ,10 β ,13 α)-4-acetoxy-13-((2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl}oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate compound of formula-1, comprising of;

- a) Reacting the 7,10-di-Troc-10-DAB compound of formula-11 with (4R,5S)-3-(tert-butoxycarbonyl)-2,2-dimethyl-4-phenyloxazolidine-5-carboxylic acid compound of formula-12 in presence of dicyclohexyl carbodiimide and 4-dimethylamino pyridine in a mixture of toluene and dichloromethane to provide compound of formula-13,
- b) deprotecting the compound of formula-13 by treating it with Zn in a mixture of acetic acid and acetone to provide compound of formula-14,
- c) methylating the compound of formula-14 by reacting with dimethyl sulfate in presence of sodium hydroxide in a mixture of toluene and tetrahydrofuran to provide compound of formula-15,
- d) treating the compound of formula-15 with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in combination with trifluoroacetic acid in dichloromethane to provide compound of formula-1.

Cabazitaxel obtained by the present invention was analyzed by HPLC under the following conditions;

Apparatus: A liquid chromatographic system equipped with variable wavelength UV detector; Column: Sunfire C18, 150×4.6 mm and 3.5µm or equivalent; Flow rate: 1.5 mL/min; Wavelength: 230 nm; Column temperature: 45°C; Injection volume: 10 µL; Run time: 45 min; Elution: gradient; Buffer: Weigh about 1.36 gm of potassium dihydrogen phosphate and 2.0 gm of 1-octane sulfonic acid sodium salt anhydrous in 1000 mL of milli Q water and adjust its pH to 2.0 with dil.ortho phosphoric acid and filtered the solution through 0.45µm Nylon membrane filter paper; Mobile phase-A: Buffer; Mobile phase-B: Acetonitrile: water (90:10, v/v); Diluent: Acetonitrile: water (50:50 v/v).

Cabazitaxel produced by the process of the present invention can be further micronized or milled to get the desired particle size to achieve desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction include, but not limited to ball, roller and hammer mills, and jet mills. Milling or micronization may be performed before drying, or after the completion of drying of the product.

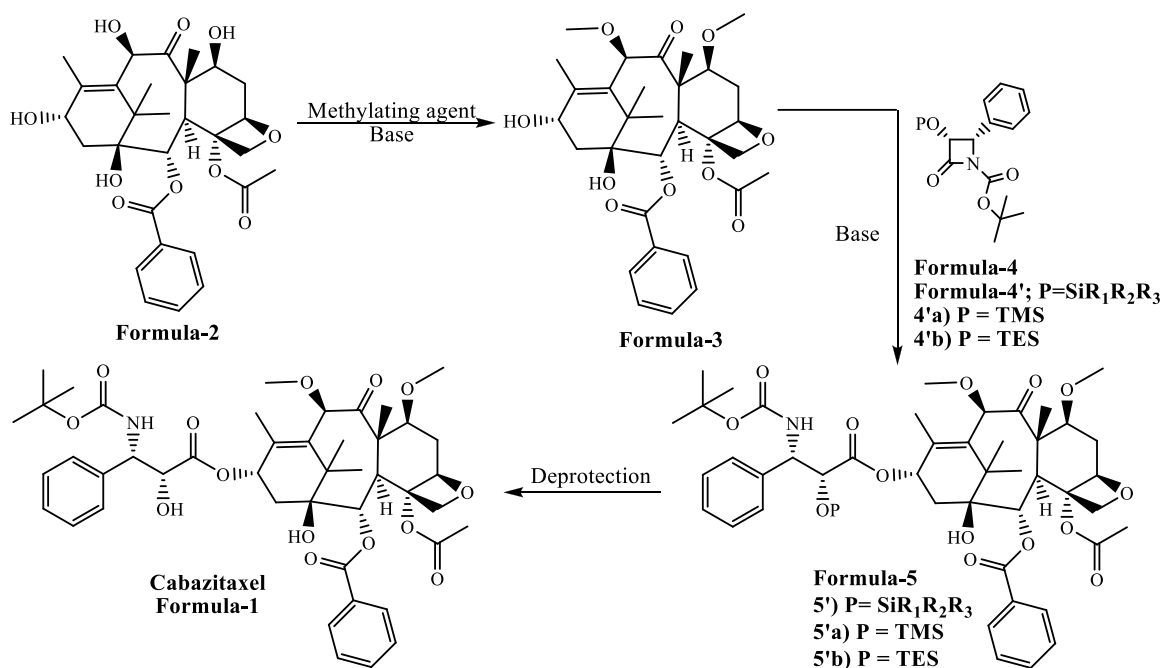
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The present invention is schematically represented as follows.

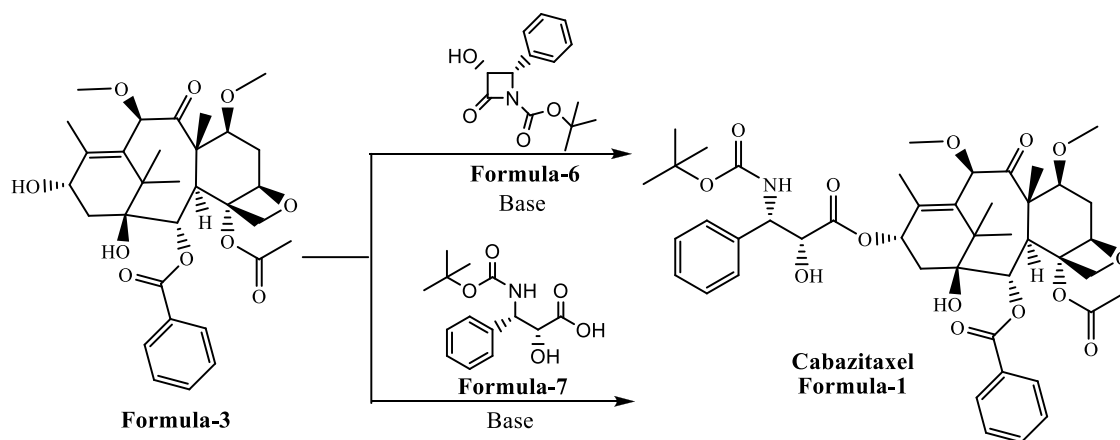
Scheme-I:

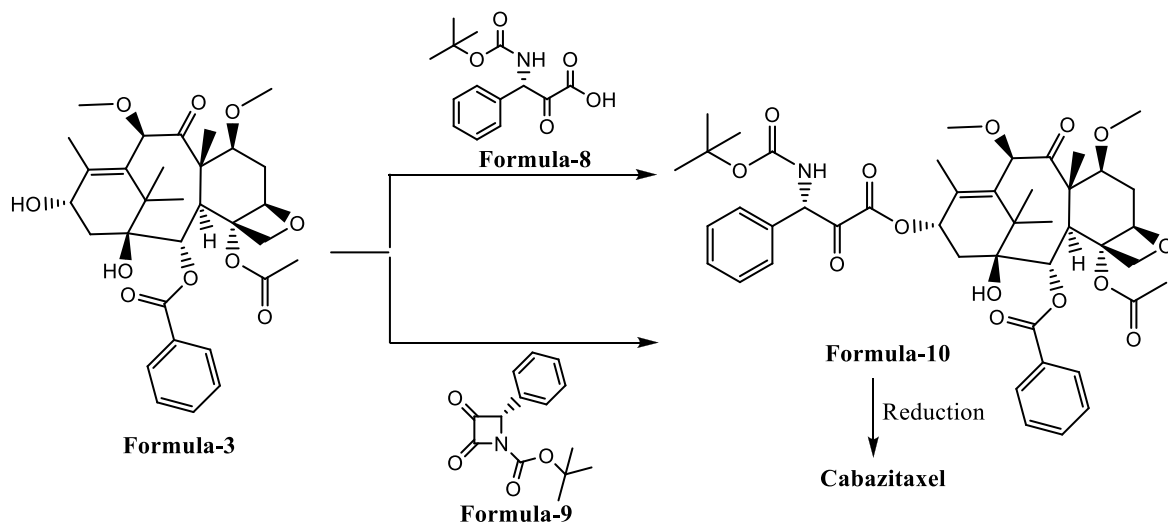
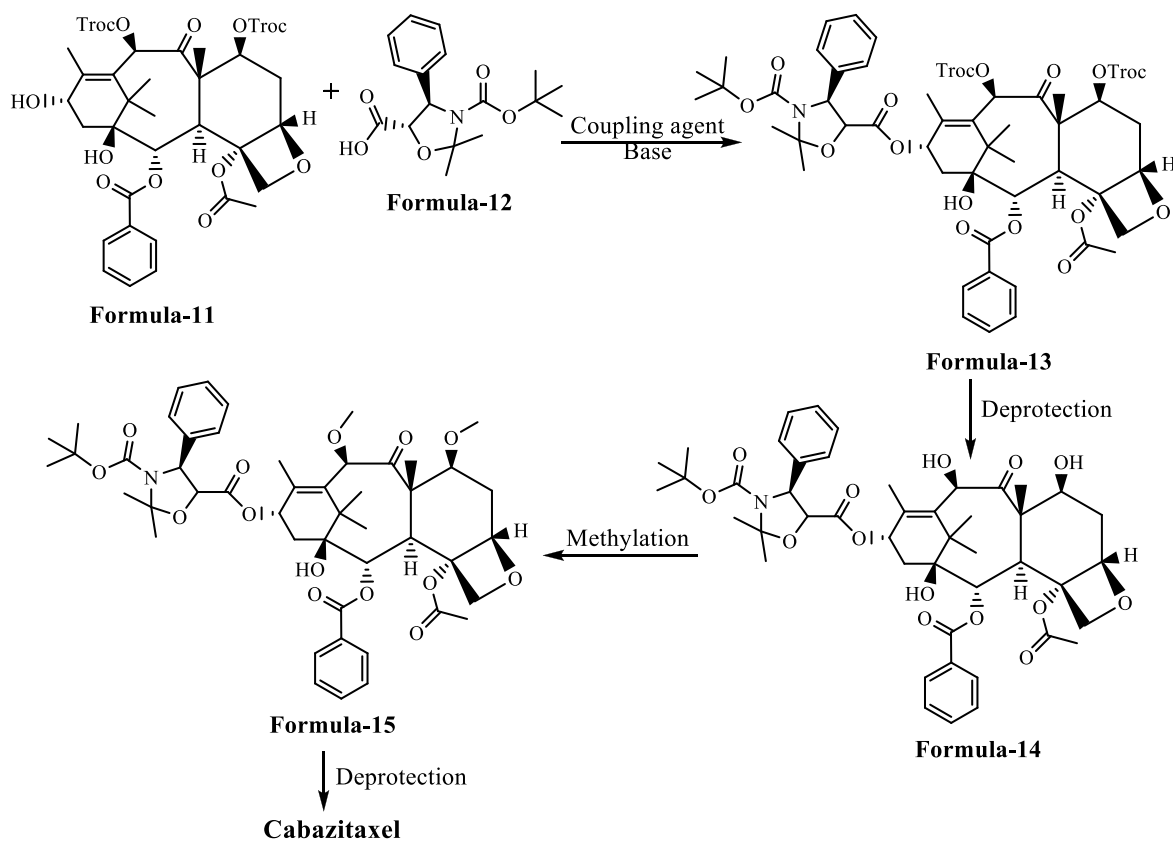


Wherein, 'P' represents hydroxy protecting group;

R_1 , R_2 & R_3 are independently selected from C_1 - C_6 straight chain or branched chain alkyl groups.

5 **Scheme-II:**



Scheme-III:**Scheme-IV:**

Examples:

Example-1: Preparation of 7,10-dimethoxy-10-DAB (Formula-3)

10-deacetylbaaccatin III compound of formula-2 (50 gm) was added to a reaction mixture of dimethyl sulfate (91.77 gm) in tetrahydrofuran (150 ml) at -5°C to 0°C. Sodium hydroxide (14.65 gm) and water (250 ml) were added to the reaction mixture at -5°C to 0°C. Raised the temperature of the reaction mixture to 5-10°C and stirred the reaction mixture for 3 hrs at the same temperature. The reaction mixture was slowly added to 10-15°C pre-cooled mixture of water (700 ml) and diisopropyl ether (1000 ml) and stirred for 45 min at the same temperature. Filtered the precipitated solid and washed with a mixture of diisopropyl ether and water. Acetone (75 ml) was added to the obtained wet compound at 20-25°C and stirred for 45 min at the same temperature. Filtered the solid, washed with acetone and dried to get the title compound.

Yield: 35.0 gm.

Example-2: Preparation of 7,10-dimethoxy-10-DAB (Formula-3)

10-deacetylbaaccatin III compound of formula-2 (50 gm) was added to a mixture of dimethyl sulfate (92.6 gm) in tetrahydrofuran (150 ml) at -5°C to 0°C. Sodium hydroxide (18.36 gm) and water (6.5 ml) were added to the reaction mixture at -5°C to 0°C. Raised the temperature of the reaction mixture to 5-10°C and stirred for 3 hrs at the same temperature. The reaction mixture was slowly added to 10-15°C pre-cooled mixture of water (500 ml) and diisopropyl ether (500 ml) and stirred for 2 hrs at the same temperature. Filtered the precipitated solid and washed with diisopropyl ether followed by with acetone. Methanol (175 ml) was added to the obtained solid at 25-30°C, heated the reaction mixture to 55-60°C and stirred for 90 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 90 min at the same temperature. Filtered the solid, washed with diisopropyl ether and dried to get the title compound.

Yield: 36.0 gm.

Example-3: Preparation of 7,10-di-Troc-10-deacetylbaaccatin-III (Formula-11)

10-Deacetylbaaccatin III compound of formula-2 (40 gm) and pyridine (200 ml) were charged into a clean and dry RBF under nitrogen atmosphere at 25-30°C and stirred the

reaction mixture for 15 min at the same temperature. A solution of 2,2,2-trichloroethoxycarbonyl chloride (35.4 ml) in dichloromethane (800 ml) was slowly added to the reaction mixture at 20-25°C under nitrogen atmosphere and stirred the reaction mixture for 15 min at the same temperature. Water was slowly added to the reaction mixture at 20-25°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and the organic layer was washed with acetic acid solution, aq.sodium bicarbonate solution, water and then with sodium chloride solution. Distilled off the solvent completely from the organic layer under reduced pressure. Petroleum ether (160 ml) was added to the obtained compound at 35-40°C and stirred for 15 min at the same temperature. Slowly cooled the reaction mixture to 0-5°C and stirred for 45 min at the same temperature. Filtered the precipitated solid, washed with petroleum ether and then dried to get the title compound.

Yield: 64.0 gm.

15 **Example-4: Preparation of compound of formula-13**

A mixture of 7,10-Ditroc-10-Deacetylbaaccatin-III compound of formula-11 (60 gm), toluene (1200 ml), dichloromethane (300 ml) and (4R,5S)-3-(tert-butoxycarbonyl)-2,2-dimethyl-4-phenyloxazolidine-5-carboxylic acid compound of formula-12 (36.6 gm) was cooled to 20-25°C. Dicyclohexyl carbodiimide (36.5 gm) and 4-dimethylamino pyridine (7.5 gm) were added to the reaction mixture at 20-25°C and stirred for 1 hr at the same temperature. Filtered the reaction mixture and washed the filtrate with aq.sodium bicarbonate solution, water followed by with sodium chloride solution. Both the organic and aqueous layers were separated and distilled off the solvent from the organic layer under reduced pressure up to 110-130 ml remains in the flask. Filtered the reaction mixture and added the filtrate to n-heptane (1500 ml) at 20-25°C and stirred for 45 min at the same temperature. Filtered the precipitated solid, washed with n-heptane and dried to get the title compound.

Yield: 72.6 gm.

Example-5: Preparation of compound of formula-14

A mixture of compound of formula-13 (150 gm), acetone (1500 ml), acetic acid (150 ml) and Zinc dust (65.6 gm) was stirred for 90 min at 25-30°C. Filtered the reaction mixture through hyflow bed and washed the hyflow bed with acetone. The obtained filtrate was

added to pre-cooled water at 5-10°C and stirred for 60 min at the same temperature. Filtered the precipitated solid and washed with water. Dichloromethane was added to the obtained wet compound at 25-30°C and stirred for 10 min at the same temperature. Both the organic and aqueous layers were separated and distilled off the solvent completely from the organic layer under reduced pressure. Acetonitrile (300 ml) was added to the obtained solid at 25-30°C. Diisopropyl ether (3000 ml) was slowly added to the reaction mixture at 25-30°C and stirred for 45 min at the same temperature. Filtered the obtained solid, washed with diisopropyl ether and then dried to get the title compound.

Yield: 98.5 gm.

Example-6: Preparation of compound of formula-15

A mixture of compound of formula-14 (140 gm), toluene (700 ml), dimethyl sulfate (250 gm) was cooled to 0-5°C and stirred the reaction mixture for 10 min at the same temperature. Sodium hydroxide (48.2 gm) and toluene (700 ml) were added to the reaction mixture at 0-5°C and stirred for 3 hrs at the same temperature. Tetrahydrofuran (70 ml) was added to the reaction mixture at 0-5°C and stirred for 90 min at the same temperature. The reaction mixture was added to pre-cooled water at 0-5°C. Ethyl acetate was added to the reaction mixture at 0-5°C and stirred for 10 min at the same temperature. Both the organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate. Combined the organic layers and washed with aq.sodium bicarbonate solution, sodium chloride solution followed by with water. Distilled off the solvent completely from the organic layer under reduced pressure and co-distilled with isopropyl alcohol. Isopropyl alcohol (140 ml) and diisopropyl ether (350 ml) were added to the obtained compound at 25-30°C. Cooled the reaction mixture to 0-5°C and stirred for 90 min at the same temperature. Filtered the solid and washed with diisopropyl ether. Methanol (140 ml) was added to the wet solid at 25-30°C and stirred for 10 min at the same temperature. Diisopropyl ether (980 ml) was added to the reaction mixture. Cooled the reaction mixture to 0-5°C and stirred for 90 min at the same temperature. Filtered the solid, washed with diisopropyl ether and then dried the material to get the title compound.

Yield: 92.5 gm.

Example-7: Preparation of compound of formula-15

A mixture of compound of formula 3 (30 gm), dichloromethane (750 ml), oxazolidine carboxylate (30.3 gm), dicyclohexyl carbodiimide (30.2 gm) and dimethyl amino pyridine (3.75 gm) was stirred for 4 hours at 25-30°C. Filtered the reaction mixture and washed with dichloromethane. The obtained filtrate was washed with aqueous sodium bicarbonate solution, with water and followed by with 20% aqueous sodium chloride solution. Distilled off the solvent from the filtrate up to the volume of the reaction mixture reaches to 150 ml - 200 ml. Filtered the reaction mixture and the obtained filtrate was slowly added to n-heptane (750 ml) and stirred the reaction mixture for 2 hours at 25-30°C. Filtered the precipitated solid and washed with n-heptane. Dry the material to get the titled compound.

Yield: 46 gm.

Example-8: Preparation of (2 α ,5 β ,7 β ,10 β ,13 α)-4-acetoxy-13-((2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl)oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate (Formula-1)

A mixture of compound of formula-15 (90 gm) and dichloromethane (270 ml) was cooled to -25°C to -30°C. Trifluoroacetic acid (180 ml) and trimethylsilyl trifluoromethanesulfonate (TMSOTf; 11.4 gm) were added to the reaction mixture at -25°C to -30°C and stirred for 4 hrs at the same temperature. Sodium bicarbonate and pre-cooled water were added to the reaction mixture at -25°C to -30°C. Dichloromethane was added to the reaction mixture and stirred for 5 min. Both the organic and aqueous layers were separated and washed the organic layer with aqueous sodium bicarbonate solution followed by with water. Distilled off the solvent completely from the organic layer under reduced pressure. Purification of the compound by silica gel column chromatography using a mixture of ethyl acetate and dichloromethane as eluent provided the title compound as an amorphous solid; Yield: 42.1 gm.

Example-9: Purification of compound of formula-1

A mixture of compound of formula-1 (55 gm) and methanol (550 ml) was stirred for 10 min at 25-30°C. Filtered the reaction mixture and distilled off the solvent from the filtrate under reduced pressure until the volume of the reaction mixture becomes 300 ml.

Dichloromethane (165 ml) was added to the reaction mixture and stirred for 10 min. Distillation of the solvent from the reaction mixture under reduced pressure followed by drying of the obtained compound provided the title compound as an amorphous solid.

Yield: 51.6 gm; Purity by HPLC: 99.97%; 10-DAB impurity: Not detected; Di-Troc impurity: Not detected; Di-Troc oxazolidine impurity: Not detected; De-Troc oxazolidine impurity: Not detected; Amine impurity: 0.02%; Oxazolidine protected Cabazitaxel impurity: 0.01%.

Example-10: Preparation of compound of formula-1

30 gm of compound of formula-15 (30 gm) was added to formic acid (150 ml) at 8-12°C and stirred the reaction mixture for 10 minutes. Raised the temperature of the reaction mixture to 25-30°C and stirred for 7 hours at the same temperature. 900 ml of pre-cooled (10-15°C) water and 150 ml of dichloromethane were added to the reaction mixture and stirred for 10 minutes. Separated the both aqueous and organic layers. Basifying the aqueous layer with aq. Sodium bicarbonate solution and 150 ml of dichloromethane was added to it. Stirred the reaction mixture for 10 minutes and separated the both aqueous and organic layers. Combined the total organic layer and washed with aqueous sodium bicarbonate solution, with water and finally with aqueous sodium chloride solution. Distilled off the solvent completely from the organic layer and 300 ml of tetrahydrofuran was added to the obtained compound. Cooled the reaction mixture to 10-15°C and sodium bicarbonate (8.58 gm) and di tert. butyl dicarbonate (11.19 gm) were added to it. Stirred the reaction mixture for 3 hours at 10-15°C. Filtered the reaction mixture and washed with ethyl acetate (60 ml). Water (150 ml) and ethyl acetate (300 ml) were added to the obtained filtrate and stirred the reaction mixture for 5 minutes. Separated the both aqueous and organic layers and aqueous layer was extracted with ethyl acetate. Combined the total organic layers and washed with water. Distilled off the solvent completely from the organic layer under reduced pressure. Purification of the compound by silica gel column chromatography using a mixture of ethyl acetate and dichloromethane as eluent provided the title compound as an amorphous solid. Yield: 14.3 gm.
